REMARKS

Claims 6 and 12-16 are pending in the application. Claims 6 and 12-16 stand rejected. By this amendment, claims 6 and 12-15 have been amended.

35 U.S.C. § 112, second paragraph rejections

1. Regarding accord with preamble

Claims 6 and 12-16 stand rejected under 35 U.S.C.§ 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Examiner states that, while other aspects of the previous 35 USC 112(b) rejection have ben overcome, Applicant has not addressed the rejection that the outcome stated in the preamble is not recited in the body of the claim. The preamble of claim 6 recites that the method is one for "inhibiting repair of double-stranded breaks in DNA in a cell". Claim 6 has hereby been amended to recite that introduction into the cell of the DNA recited in the claim results in inhibition of repair of double-stranded breaks in DNA in said cell. Thus, the outcome stated in the preamble is now recited in the body of the claim. Applicant submits that this amendment does not constitute the addition of new matter, since the amended recitation is merely taken from the language used in the preamble of the claim, thus overcoming this rejection.

2. Regarding New Rejections

Claims 6 and 12-16 stand rejected under 35 USC 112(b) due to the recitation of the word "containing" in the claims when referring to the presence of the ORFs located on the DNA that is utilized in the methods of the invention. Examiner states that the meaning of this word is indefinite, and suggests use of the word "comprising" (or "consisting of) instead. Claims 6 and 12-15 have hereby been amended to recite "comprising" instead of "containing", thus overcoming this rejection.

35 U.S.C. §103 (a) rejection

Vollmer et at. Claims 6 and 12-16 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Vollmer et al. Claim 6 recites a method of inhibiting repair of double-stranded breaks in DNA in a cell. The method comprises introducing into the cell DNA comprising early region 4 (E4) open

reading frame 6 (ORF6) and E1B region of genomic adenoviral DNA. According to the method, the gene products of the two regions are expressed in the cell in a quantity sufficient to inhibit repair of double-stranded breaks in DNA in the cell. Claim 12 is a similar claim, but the inhibition of the repair of double-stranded breaks in DNA occurs in a cancer cell and is coupled with chemotherapy.

The Examiner states that Vollmer et al. discloses a method of improving the efficiency of chemotherapeutic agents with adenovirus E4 orf6 in mice. Applicant submits that this analysis of the work presented by Vollmer et al. is incorrect. In fact, Vollmer et al. are, (curiously, as correctly stated by Examiner), completely silent regarding E4orf6. Vollmer et al. neither show nor discuss the use of E4orf6 for any purpose, and in particular, Vollmer et al. do not test the ability of E4orf6 or any other adenoviral gene products to inhibit repair of breaks in ds DNA as recited in claims 6 and 12. Rather, Vollmer et al. discuss methods of improving the efficiency of chemotherapeutic agents in tumor cells of a specific type (p53 negative tumor cells) with adenoviruses (the entire adenovirus) except that it lacks a functional E1B gene product.

In order for the method of augmenting chemotherapy described by Vollmer et al. to work, the adenovirus must replicate within the cancer cell and kill the cancer cell. The use of adenoviruses lacking a functional E1B gene product was purposeful. The idea was to attempt to selectively kill tumor cells that were p53 negative, as many tumor cells are. p53 is known to inhibit viral replication, and the E1B gene product inhibits p53, i.e. viruses with active E1B can replicate in p53 positive cells. The absence of active p53 in cell permits viral replication and cell death, with or without E1B. The hope was that adenoviruses lacking EIB would replicate freely in p53 negative tumor cells and kill these tumor cells, but would be unable to infect and replicate in healthy, p53 positive cells, thereby providing a method of selectively killing p53 negative tumor cells.

Thus, the Examiner's statement that Vollmer et al. use a method of improving the efficiency of chemotherapeutic agents with adenovirus E4 orf6 is incorrect. It follows then that Examiner's suggestion of introducing E1B back into the adenovirus utilized by Vollmer et al. is illogical. Technically, this would consist of reintroduction of E1B whihc would essentially reconstruct the wild type virus. This would simply recreate the original wild type phenotype! Any

possibility of selective killing of p53 negative tumors, as taught by Vollmer et al., would be nullified. Applicant submits that there is no showing or suggestion in Vollmer et al. regarding the use of E4 orf-6 to improve the efficiency of chemotherapy, and certainly no suggestion or showing of improving the :results obtained by Vollmer et al. by adding E1B back to the virus. Such a suggestion runs counter to the goal of Vollmer et al., and would render the adenovirus useless for his purpose (selectively killing p53 negative tumor cells.

Applicant also notes that claim 6 does not recite a method of increasing the efficacy of chemotherapeutic agents. Thus, the methodology of Vollmer et al. is irrelevant to the subject matter of claim 6. As stated above, Claim 6 recites a method of inhibiting repair of double-stranded breaks in DNA in a cell by introducing into the cell DNA comprising early region 4 (E4) open reading frame 6 (ORF6) and E1B region of genomic adenoviral DNA. Expression of the gene products of the two regions results in inhibition of repair of double-stranded breaks in DNA in the cell. Applicant notes that, in contrast to the method described by Vollmer et al., viral replication is not recited in the claim, and is not necessary to carry out the method. The DNA does not even have to be located in an adenovirus, but may, for example, be . on a plasmid (see page 25, lines 34-35 of the specification).

Claim 12 does recite a method for chemotherapeutic or radiation treatment of cancer. However, the method has nothing to do with that taught by Vollmer et al. Rather, like claim 6, the method involves the inhibition of repair of double-stranded breaks in DNA in the cell by the gene products of E4 orf-6 and E1B. Applicant submits that Vollmer et al. neither show nor discuss the repair of double-stranded breaks in DNA, and neither show nor discuss the use of the gene products of E1B and E4 orf-6 in such repair. In fact, E4orf-6 is never alluded to by Vollmer et al. Thus, the use of the gene products of E1B and E4 orf-6 to inhibit repair of double-stranded breaks in DNA as recited in claims 6 and 12 cannot be rendered obvious by Vollmer et al.

Ramalingam et al. and Vollmer et al. in combination. Claim 6 stands rejected under 35 U.S.C. §103(a) as unpatentable over Ramalingam et al. in combination with Vollmer et al. Examiner states that Ramalingam et al. disclose an adenovirus that expresses E4 orf 6 and that while silent on the exact effect of E4ORF6, the method involves the same step of introducing into the cell the gene product of E4ORF6 by way of adenovirus infection. Applicant respectfully notes that the

method of claim 6 of the present invention does not recite introduction of the gene product of E4 orf 6 by way of adenovirus infection. An infection by an adenovirus is not necessary for the practice of the present invention. The DNA that encodes the gene products of interest may be introduced into the cell by any suitable means. The point of the present invention is to cause the gene products of both E4 orf-6 and E1B to be present in the cell at the same time, in an amount sufficient to inhibit the repair of double-stranded breaks in DNA.

Examiner states that Ramalingam et al. are silent on the exact effect of E4orf-6. However, Applicant submits that they are not silent on the observation that forms the topic of the publication: the presence of an adenovirus with E4 orf-6 and lacking E1B significantly prolongs the survival of primary human endothelial cells. The E1-E4+ vector provided an "antiapoptotic" signal to the cells, and the cells were put into a growth-factor free and serum-free state of "suspended animation". (See abstract, and entire second paragraph of the article.)

Examiner states that it would have been obvious for one of skill in the art to add the E1B region back to the vector used by Ramalingam et al. which achieves these life-extending effects. Applicant strongly disagrees. Applicant submits that one of skill in the art, upon knowing of the experimental results of Ramalingam et al., would not choose the vector employed by Ramalingam et al. as a starting point for development of a gene combination to carry out methods in which it was desired to inhibit the repair of breaks in double-strand DNA. There is no discussion of the repair of double-strand DNA breaks in Ramalingam et al. and there is no showing or suggestion of "adding back" the E1B region, or that such an "adding back" would produce a useful vector. E1B is taught by Vollmer et al. to allow viral transcription in p53 positive cells. The combination of the attributes shown by the vector of Ramalingam et al. (prolongation of cell survival) and the ability replicate in p53+ cells would have been predicted to result in a vector that replicated freely in p53+ cells, and yet somehow prolonged the life of the cells. Applicant submits that this is illogical.

Claim 6 recites a method of inhibiting the repair of double-strand breaks in DNA using two specific regions of the adenoviral genome, the gene products of which are together sufficient to inhibit DS break repair. Applicant submits that neither reference cited by the Examiner shows or suggests that these regions, either alone or in combination, are capable of inhibiting DS break

repair. This is not surprising since it is the present inventors who discovered the phenomenon. Neither Vollmer et al. nor Ramalingam et al. were aware of this, and in fact the data presented by Ramalingam et al. taken at face value contradicts this idea, since he observed the prolongation of life in cells infected with an El-E4+ vector. The combination suggested by Examiner would result in reconstituting a virus with a wild type phenotype, i.e. a virus that could replicate in and kill any cell, thereby defeating the method of Ramalingam et al., which prolongs cell life.

In summary, neither Vollmer et al. alone, or Ramalingam et al. in combination with Vollmer et al., (both taken in light of knowledge extant in the field at the time of filing of the present application), could render obvious claims 6 and 12- 16 of the present application. Further, neither reference provides motivation for one of skill in the art to "add back" E1B to the El-E4+ vector. Rather, based on these references, one would be motivated not to add back E1B because the purpose of the work presented in either reference would then be defeated.

In view of the foregoing, reconsideration and withdrawal of these rejections are respectfully requested.

Other matters.

Claims 6 and 12 have hereby been amended to recite that the gene products of early region 4 (E4) open reading frame 6 (ORF6) and said E1B region of genomic adenoviral DNA are expressed after the DNA encoding them is introduced into the cell, and further, that they are expressed in a quantity sufficient to inhibit repair of double-stranded breaks in DNA in the cell. Support for this amendment can be found in the specification, for example on page 25 at lines 34-35 where introduction of DNA and expression of gene products is discussed. The language related to sufficiency was already in claim 12, and claim 6 has hereby been amended to recite similar language, providing accord between the two claims. The specification refers to sufficiency on page 42, line 35. Applicant thus submits that these amendments do not constituted the introduction of new matter, and respectfully requests entry of these amendments.

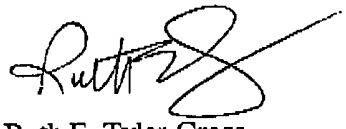
Formal Matters and Conclusion

In view of the foregoing, Applicant submits that all rejections have been successfully traversed. The Examiner is respectfully requested to pass the above application to issue at the earliest possible time.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at the local telephone number listed below to discuss any other changes deemed necessary in a telephonic or personal interview.

Please charge any underpayment or credit any overpayment of fees to attorney's deposit account # 50-2041.

Respectfully submitted,



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